Association Between Depression and Vascular Disease in Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease with increased prevalence of cardiovascular disease (CVD) and depression. Although depression may contribute to CVD risk in population-based studies, its influence on cardiovascular morbidity in SLE has not been evaluated. We evaluated the association between depression and vascular disease in SLE.

Methods. A cross-sectional study was conducted from 2002-2005 in 161 women with SLE and without CVD. The primary outcome measure was a composite vascular disease marker consisting of the presence of coronary artery calcium and/or carotid artery plaque.

Results. In total, 101 women met criteria for vascular disease. In unadjusted analyses, several traditional cardiovascular risk factors, inflammatory markers, adiposity, SLE disease-related factors, and depression were associated with vascular disease. In the final multivariable model, the psychological variable depression was associated with nearly 4-fold higher odds for vascular disease (OR 3.85, 95% CI 1.37, 10.87) when adjusted for other risk factors of age, lower education level, hypertensive status, waist-hip ratio, and C-reactive protein.

Conclusion. In SLE, depression is independently associated with vascular disease, along with physical factors. (First Release Dec 15 2011; J Rheumatol 2012;39:262–8; doi:10.3899/jrheum.110327)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS CARDIOVASCULAR DISEASE DEPRESSION
CALCIFICATION CAROTID PLAQUE PSYCHOSOCIAL FACTORS

Depression and cardiovascular disease (CVD) are among the most prevalent and disabling conditions worldwide, contributing to the global public health burden[1]. Patients diagnosed with heart disease are at increased risk for developing depression up to 8 years after medical diagnosis[2]. In populations initially free of cardiac disease, depression increases risk for subclinical atherosclerosis by greater than 2-fold[3,4], and risk for incident cardiac events by 50% or more[5,6], including a 4.5-fold increased risk for myocardial infarction (MI)[7]. In patients with existing CVD, the presence of depression increases the risk of future cardiac events[8], and increases risk of mortality up to 5 years following first MI[9].

Systemic lupus erythematosus (SLE) is a chronic systemic inflammatory autoimmune disease characterized by high rates of both CVD and depression. Young female patients with SLE have a 50-fold increased risk of MI compared to women without lupus[10], and higher than expected rates of stroke and hypertension[11]. Markers of subclinical atherosclerosis, such as coronary artery calcium (CAC) and carotid plaque, are also more prevalent in women with SLE[12,13]. These atherosclerotic markers predict future cardiac events in SLE[14] and therefore serve as surrogates for CVD. Notably, although all-cause mortality rates in patients with SLE have decreased in recent decades, CVD-related mortality has not[15]. Thus, understanding and treating the risk factors for CVD in SLE is important.

Investigations have shown that traditional CV risk factors such as hypertension, hyperlipidemia, and high body mass index (BMI)[16,17,18] are associated with increased rates of atherosclerotic changes in SLE. However, the presence of tradi-

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tional risk factors alone does not fully explain the greatly increased risk for CVD in SLE.

In addition to traditional CVD risk factors, it has been clearly shown that a "lupus factor" related to SLE disease or its treatment is an important contributor to atherosclerotic changes and CVD in SLE[19,20]. Longterm use of corticosteroids, high levels of inflammation, and accrued organ damage due to immune activation are some of the potential "lupus factor" candidates contributing to CVD in this group.

Depression may play a role in lupus as well as in CVD. Depression is more prevalent in patients with SLE than in controls and in patients with other inflammatory conditions such as rheumatoid arthritis and ankylosing spondylitis[21,22,23]. There is some evidence that depression is associated with SLE disease activity[22,23,24]. Depression is associated with poor medication adherence among SLE patients[25] as well as cognitive impairment[26,27]. Although studies of CVD in SLE frequently include disease-related variables, the potential role of depression has received little attention.

We evaluated psychological as well as biological factors associated with atherosclerosis in SLE, a chronic inflammatory disease with high rates of CVD, mental health concerns, and traditional biological and demographic patterns commonly associated with poor heart health.

MATERIALS AND METHODS

Study population. The participants in this study were women with SLE enrolled in the Heart Effects on Atherosclerosis and Risk of Thrombosis in SLE (HEARTS) investigation, funded by the National Institutes of Health (R01 AR46588). The purpose of the HEARTS study was to compare prevalence and risk factors for coronary artery calcification in women with SLE and healthy controls. The participants had no history of CVD events[28] and were nonselectively recruited from the Pittsburgh Lupus Registry, which at the time of enrollment included 983 living participants. The registry includes patients seen at inpatient or outpatient facilities at the University of Pittsburgh Medical Center or by practicing rheumatologists within the Pittsburgh metropolitan area. All women with SLE were required to fulfill 1982 or 1997 American College of Rheumatology (ACR) revised criteria for the classification of definite or probable SLE[29,30] and be over the age of 18 years.

All participants completed informed consent procedures. The study was approved by the University of Pittsburgh Institutional Review Board.

Procedures. The study procedures included an interview, completion of a validated depression questionnaire [the Center for Epidemiologic Studies Depression Scale (CES-D)][31], physical examination, and laboratory and imaging studies [electron beam computed tomography (EBT) and carotid ultrasound]. Each participant completed the study procedures during a single study visit. Data for this cross-sectional study were collected between March 2002 and September 2005.

Traditional cardiovascular risk factors. Information was collected on age, patient-reported race, education level, smoking habits, family history of CVD (MI, stroke, or sudden death of a first-degree relative before age 60 yrs), waist and hip circumference, and BMI. Blood pressure was determined and hypertension was defined as blood pressure > 140 mm Hg systolic or > 90 mm Hg diastolic or the use of antihypertensive therapy. Fasting blood samples were obtained for standard laboratory testing of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, insulin, albumin, homocysteine, and glucose levels. Insulin resistance was calculated using the homeostatic model formula[32,33]: [insulin (mU/l) × glucose (nmole/l)]/22.5.

Inflammatory markers. Laboratory assessments of inflammatory markers were conducted using blood samples from the single study visit. Assays were run in batches to reduce analytical variability. Soluble E-selectin (sE-selectin) and soluble intercellular adhesion molecule-1 (sICAM-1) were measured by commercial assays (Parameter Human sE-Selectin Immunoassay and Human sICAM-1 Immunoassay; both from R&D Systems, Minneapolis, MN, USA). High sensitivity C-reactive protein (hsCRP) was quantified by automated particle-enhanced immunonephelometry (BN-II, Siemens Healthcare Diagnostics, Deerfield, IL, USA). Fibrinogen was measured using an automated clot-rate assay (Diagnostica Stago STA-R, Parsippany, NJ, USA)[34,35] (R.P. Tracy, University of Vermont).

SLE-related factors. Rheumatologists specializing in SLE (AHK, SM) assessed disease activity and cumulative organ damage due to SLE at the study visit. Measures included the revised Systemic Lupus Activity Measure (SLAM-R)[36] and the SLE Disease Activity Index (SLEDAI)[37]. The SLAM-R assesses disease activity in 11 organ systems occurring over the previous month, with possible score range 0–81. The SLEDAI contains weighted descriptors of SLE signs and symptoms present in the past 10 days, and the score can range from 0 to 105. Organ damage due to SLE was measured using the Systemic Lupus International Collaborating Clinics (SLICC) damage index[38] with the vascular items removed, yielding a possible score range of 0–36. We also collected information regarding individual criteria for SLE diagnosis and history of steroid use.

Psychosocial assessment. Participants completed the CES-D during the study visit. The CES-D is a validated 20-item self-report instrument used extensively in community samples and medically ill groups, including SLE[21,39,40,41]. The CES-D items assess past-week symptoms, such as persistent sadness, low motivation, and feelings of worthlessness, that are consistent with a depressive disorder. Although the CES-D is not used to diagnose specific depressive disorders, clinically significant depression is typically defined as a CES-D score > 16[31,42]. We used a CES-D symptom score > 16 as the indicator of clinically significant depression.

Vascular disease endpoint. The vascular disease indicator for the study was a composite consisting of presence of CAC and/or carotid artery plaque. Such composites are accepted practice in atherosclerosis and CV event research[43,44]. The first step in determining the composite vascular disease indicator was to measure for the presence of CAC using EBT (Imatron C-150 scanner; Imatron, San Francisco, CA, USA). Thirty to forty 3-mm slices starting at the aortic root to the apex of the heart were scanned in all participants at the same point during diastole (80% of the RR interval in the electrocardiogram) during a single breath-hold. The images were scored for calcification using the Agatston method[45]. Presence of CAC was defined as Agatston score > zero. For carotid artery plaque, the carotid ultrasound methodology has been described[16]. A Toshiba SSA-270A scanner (Toshiba, Tustin, CA, USA) equipped with a 5-MHZ linear array imaging probe was used to image the carotid arteries. Sonographers scanned the right and left common carotid artery, carotid bulb, and the first 1.5 cm of the internal and external carotid arteries. Plaque was defined as a distinct area protruding into the vessel lumen that was at least 50% thicker than the surrounding areas. For each area scanned, the degree of plaque was graded 0 (no observable plaque) to 3 (plaque covering ≥ 50% of the vessel diameter); grades were summed across the right and left carotid arteries to create an overall measure of focal plaque extent, called the plaque index. The plaque index has been found to be a reproducible and valid measure of carotid atherosclerosis in a number of populations[46]. For the current study, the presence of carotid plaque was defined as plaque index ≥ 1.

Data analysis. We checked the quality of the data by evaluating the frequency distribution of all relevant variables, and assessed for multicollinearity among the variables. Continuous variables were summarized as mean (SD) and categorical variables as percentages (n). Continuous variables that had skewed distribution, such as waist-hip ratio, were transformed into quartiles. The primary outcome measure was a binary variable indicating vascular disease, defined as presence of CAC and/or carotid artery plaque. Logistic regression was used to evaluate the univariate associations between each of

the traditional, inflammatory, psychological, and SLE-related factors and the presence or absence of vascular disease. Variables associated with vascular disease in the univariate analyses were considered for inclusion in the multivariable logistic regression model, based on the variable selection methodology described in Vittinghoff[47]. To select variables for inclusion in multivariable models, we first chose those found to be significant ($p < 0.15$) in unadjusted single predictor models. Each of these variables was evaluated systematically for inclusion in the multivariable logistic regression model[48], and was retained or removed based upon Akaike information criteria (AIC). The systematic evaluation of variables for inclusion was an iterative process. An example of the iterative process would be starting with important variables such as age and hypertension in the model, inflammatory variables may be added one by one, their significance assessed, and AIC evaluated to determine which inflammatory marker or sets of inflammatory markers fits best in the model or whether they should be removed. Then SLE variables would be considered, one by one, in a similar fashion, and the model would be evaluated with and without the inflammatory variable or variables. Variable inclusion and removal proceeds in this fashion until all significant univariate variables have been considered. The adequacy of the final multivariable model was evaluated using the specification link test and Hosmer-Lemeshow goodness-of-fit test. SPSS 15 (SPSS Inc., Chicago, IL, USA) and Stata 9 (Intercooled Stata 9.1; StataCorp LP, College Station, TX, USA) were used to perform all statistical analyses. The final model was checked for interaction effects.

RESULTS

Clinical and demographic characteristics. One hundred sixty-one women with SLE were enrolled in the study and completed the assessments. Overall mean age was 50.0 years (SD 10.0); 88% (SD 141) were white, and 55% (SD 89) were hypertensive (defined as using antihypertensive medication or having blood pressure > 140/90 mm Hg). Total cholesterol was 190 mg/dl (SD 41) and waist-hip ratio was 0.85 (SD 0.1). The mean CES-D score was 11.6 (SD 9), with 27% of the sample (43/161 women) scoring at or above 16, a score consistent with clinically meaningful depressive symptoms. Of a possible range of 0–60, the CES-D score ranged from 0 to 45 in the sample overall. We evaluated associations between depression and other characteristics using logistic regression. Older age and being in the second quartile of waist-hip ratio were marginally associated with depression ($p = 0.056$, $p = 0.078$, respectively). Depression was not associated with hypertension, race, education, cholesterol, and steroid use.

SLE characteristics. Disease-related characteristics of the SLE sample are provided in Table 1. The average length of time from SLE diagnosis was 16.3 (SD 7.0) years (range 5–47 yrs). Current SLE disease activity was mild, on average, with mean SLAM-R of 4.5 (SD 2.9, range 0–15), and mean SLEDAI was 2.0 (SD 2.3, range 1–14). Cumulative organ damage scores, i.e., SLICC-ACR Damage Index without vascular items, averaged 1.4 (SD 1.6, range 0–9). Regarding treatment with steroids, the majority of patients (110 of 161) had used steroids, with a median duration of 10 years of use.

Vascular disease and CVD risk factors. Forty-eight percent (SD 77%) of patients showed evidence of CAC, and carotid plaque was found in 36% (SD 58%). The calcium and plaque data are not shown in the tables. One hundred one (63%) of the women showed evidence of vascular disease, defined as presence of coronary calcium and/or carotid plaque. Demographic characteristics and CVD risk factors of SLE patients with and without evidence of vascular disease are shown in Table 2. Several traditional CVD risk factors were associated with vascular disease, including age, years of education, hypertension, adiposity, elevated triglyceride levels, glucose, and insulin resistance. SLE patients with vascular disease had higher mean waist-hip ratios compared to those without vascular disease (0.86 ± 0.1 vs 0.82 ± 0.1, respectively; $p = 0.03$). Further, those in the highest quartile of waist-hip ratio were more likely to have vascular disease, with an unadjusted OR of 3.99 (95% CI 1.46–10.88; $p = 0.007$). Inflammatory factors related to vascular disease were higher levels of hsCRP, sE-selectin, and fibrinogen. Depression, defined as CES-D depressive symptom score > 16, was more prevalent among SLE women with vascular disease (35%) compared to those without (15%; $p = 0.004$). CES-D scores ranged from 0 to 45 in women with vascular disease, and from 0 to 38 in those without. In terms of SLE disease characteristics, women with SLE who had evidence of vascular disease had greater cumulative damage due to SLE and longer history of corticosteroid use.

Table 1. Characteristics of patients with systemic lupus erythematosus (SLE) (n = 161).

Characteristics	Mean (SD)
Disease duration, yrs	16.3 (7.0)
SLAM-R	4.5 (2.9)
SLEDAI	2.0 (2.3)
SLICC/ACR Damage Index without vascular items	1.4 (1.6)
No. ACR criteria, median (IQR)	5 (4–7)
Skin (malar or discoid rash), %	48
Photosensitivity, %	68.6
Oral ulcer, %	60
Arthritis, %	92
Serositis, %	48
Renal, %	24.5
Central nervous system*, %	8
Hematologic, %	54
Immunologic, %	60
ANA positive, %	99

* Diagnostic criteria for CNS lupus include only seizure and psychosis. IQR: interquartile range; ACR: American College of Rheumatology; CNS: central nervous system; ANA: antinuclear autoantibody; SLAM-R: Systemic Lupus Activity Measure-Revised; SLEDAI: SLE Disease Activity Index; SLICC/ACR: Systemic Lupus International Collaborating Clinics/American College of Rheumatology.

The final multivariable model for presence of vascular disease in women with SLE included several traditional cardiovascular risk factors (age, hypertension, years of education), inflammation, adiposity, and depression (Table 3). Women in the highest quartile of waist-hip ratio (≥ 0.87) were 4 times more likely to have vascular disease, after adjustment for other risk factors. Patients with depression had nearly 4-fold increased odds for vascular disease (OR 3.85, 95% CI 1.37–10.87), independent of traditional risk factors, adiposity,

Table 2. Unadjusted logistic regression analysis of covariates of vascular disease in patients with SLE. Covariates with $p < 0.15$ were evaluated for inclusion in multivariable models. Statistically significant differences ($p < 0.05$) between SLE patients with and those without vascular disease are indicated in bold type.

Traditional Risk Factors	Vascular Disease Present*, n = 101	No Vascular Disease*, n = 60	OR (95% CI)	p
Age, yrs	53.5 (9.6)	44.5 (8.0)	**1.12 (1.07–1.17)**	**< 0.001**
White, %	87 (88)	90 (54)	0.75 (0.27–2.10)	0.586
Years of education	13.8 (2.4)	15.2 (2.6)	**0.80 (0.70–0.92)**	**0.002**
Systolic BP, mm Hg	128.3 (20.0)	109.4 (13.5)	**1.07 (1.04–1.10)**	**< 0.001**
Diastolic BP, mm Hg	78.5 (10.3)	73.3 (9.5)	**1.05 (1.02–1.09)**	**0.002**
Hypertension†, %	64 (65)	38 (23)	**2.90 (1.50–5.62)**	**0.002**
Waist-hip ratio, %				
1st quartile	11.9 (12)	23 (14)	—	—
2nd quartile	20.8 (21)	30 (18)	1.36 (0.50–3.68)	0.544
3rd quartile	26.7 (27)	27 (16)	1.97 (0.73–5.29)	0.179
4th quartile	40.6 (41)	20 (12)	**3.99 (1.46–10.88)**	**0.007**
Body mass index, kg/m^2	30.2 (6.6)	23.9 (4.1)	**1.25 (1.15–1.36)**	**< 0.001**
Ever a smoker, %	40 (40)	30 (18)	1.53 (0.77–3.02)	0.221
Homocysteine, mg/dl	10.8 (4.4)	9.8 (3.4)	1.07 (0.98–1.17)	0.130
Fasting serum glucose, mg/dl	96.1 (25.5)	86.7 (8.9)	**1.04 (1.01–1.08)**	**0.004**
Serum albumin, mg/dl	4.5 (0.52)	4.7 (0.45)	**0.50 (0.26–0.99)**	**0.046**
Total cholesterol, mg/dl	192.5 (40.8)	186.3 (41.3)	1.00 (0.99–1.01)	0.359
HDL cholesterol, mg/dl	53.6 (17.0)	55.1 (15.5)	0.99 (0.98–1.01)	0.590
LDL cholesterol, mg/dl	111 (35.7)	108.4 (30.96)	1.00 (0.99–1.01)	0.641
Triglycerides, mg/dl	144.6 (91)	114.9 (56.7)	**1.01 (1.00–1.01)**	**0.028**
HOMA insulin resistance	4.7 (5.2)	2.6 (1.9)	**1.38 (1.11–1.73)**	**0.004**
Inflammatory markers				
hsCRP, mg/dl	5.5 (6.5)	2.9 (4.3)	**1.12 (1.03–1.23)**	**0.010**
sICAM-1, ng/ml	302.8 (91.6)	276.8 (108.7)	1.00 (1.00–1.01)	0.112
sE-selectin, ng/ml	51.7 (21.2)	43.6 (20.3)	**1.02 (1.00–1.04)**	**0.023**
Fibrinogen, mg/dl	350.3 (84.8)	321 (88.1)	**1.00 (1.00–1.01)**	**0.041**
Psychological				
CES-D ≥ 16, %	35 (35)	13 (8)	**3.45 (1.47–8.06)**	**0.004**
SLE characteristics				
Duration, yrs	16.6 (6.8)	15.7 (7.4)	1.02 (0.97–1.07)	0.418
ACR criteria	5.7 (1.7)	5.5 (1.5)	1.06 (0.87–1.29)	0.581
SLICC damage index, modified††	1.6 (1.7)	1.0 (1.2)	**1.32 (1.04–1.68)**	**0.023**
SLEDAI score	2.0 (2.4)	2.0 (2.1)	1.00 (0.89–1.15)	0.999
SLAM score	4.6 (2.9)	4.5 (2.9)	1.01 (0.90–1.13)	0.833
Steroid use, ever, %	87 (88)	90 (54)	1.40 (0.52–3.77)	0.505
Steroid use, yrs	11.2 (7.6)	8.5 (5.4)	**1.07 (1.00–1.13)**	**0.047**

* Mean (SD) are provided for continuous variables, and number (%) for dichotomous variables. † Defined as blood pressure ≥ 140/90 mm Hg or taking antihypertensive medication. †† The SLICC/ACR damage index was modified by removing vascular items. SLE: systemic lupus erythematosus; BP: blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HOMA: homeostatic model; hsCRP: high sensitivity C-reactive protein; sICAM-1: soluble intracellular adhesion molecule-1; sE-selectin: soluble E-selectin; CES-D: Center for Epidemiologic Studies-Depression Scale.

and CRP. Notably, the univariate OR and CI for depression were relatively unchanged after adjustment for the other significant and relevant covariates. This finding indicates that depression has an independent role in CVD. The final model was also checked for interaction effects and there were none.

DISCUSSION

Our results indicate that both psychological and biological factors are associated with vascular disease in women with SLE. Depression is strongly associated with vascular disease, after adjusting for other traditional and inflammatory risk factors. There are several potential pathways that link depression and CVD in SLE. These pathways include possible biological mechanisms, and may also reflect behavioral and environmental influences on health.

Depression is associated with increases in proinflammatory cytokines[49,50] and the increased CVD risk in depressed persons may be related to added inflammatory burden. A recent case-control study found an elevation in the proinflammatory cytokine interleukin 6 (IL-6) in SLE, and this inflammatory factor was associated with CAC[20]. The association between depression and inflammation is likely bidirectional[51]. An

Table 3. Multivariable logistic regression analysis of risk factors for vascular disease in women with SLE (n = 161).

Variable	OR (95% CI)	p
Age	1.11 (1.06–1.17)	< 0.001
Years of education	0.82 (0.68–0.99)	0.037
Depression (CES-D ≥ 16)	3.85 (1.37–10.87)	0.011
Hypertension	2.50 (1.10–5.66)	0.028
Waist-hip ratio*		
2nd quartile, 0.77 to < 0.814	1.11 (0.32–3.94)	0.867
3rd quartile, 0.814 to < 0.868	2.60 (0.73–9.36)	0.142
4th quartile, ≥ 0.868	4.03 (1.12–14.49)	0.032
hsCRP	1.12 (1.01–1.23)	0.029

* Reference group is the first quartile of waist-hip ratio, < 0.77. For definitions, see Table 2.

inflammatory environment, which is typically present in patients with SLE, may result in low mood and malaise[52].

Depressed mood, particularly when chronic, may have a negative influence on lifestyle and behavior choices. For example, depression is a risk factor for poor medication adherence in SLE[25] and in adults with heart disease[53]. Depression may interact with physical inactivity to influence CVD. Murine studies indicate that depressed behavior induced by chronic intermittent stress led to reduced exercise and ultimately to early atherosclerotic changes[54]. In a population study of elderly men, baseline depressive symptoms were associated with physical inactivity. Ten-year risk of cardiac mortality was increased about 50% by the combined effect of depressive symptoms with inactivity[55].

We considered adiposity as a potential pathway linking depression and vascular disease. Adiposity has received attention in CVD research because adipose tissue, particularly visceral adipose tissue, is known to produce inflammatory factors. In a medically healthy group, depression was found to influence weight accumulation, which led to increased production of inflammatory cytokines[56]. In SLE, obesity was related to increased levels of CRP and IL-6, as well as reduced functional capacity[57]. Our group recently found that BMI mediated an association between depressive symptoms and CAC in SLE[58]. However, in our current study we found that even after adjusting for waist-hip ratio, itself an important risk factor, depression was strongly associated to vascular disease.

In SLE, depression can be a manifestation of central nervous system (CNS) involvement. Although the classification criteria for SLE include only history of seizures or psychosis as the indicators of neurologic involvement[30], depression is a component of neuropsychiatric lupus[59]. Mood disorders are included among the 19 central and peripheral neuropsychiatric syndromes listed in the 1999 ACR nomenclature for neuropsychiatric lupus[60].

Whether depression is linked to CVD in SLE through behavioral pathways, biological pathways, or both remains unresolved. Depression may result from the struggle to cope with a fatiguing, painful, and unpredictable chronic condition. SLE frequently is associated with work disability and loss of income, which could contribute to depression as well as to reduced ability to access healthcare. Depression and low access to healthcare may both contribute to low adherence with medical treatment, possibly resulting in increased risk of CVD. On the other hand, depression may be a product of the inflammatory milieu of SLE. To the extent that inflammation contributes not only to CVD risk directly but also, on an individual level, to feelings of malaise and low motivation, depression may be a direct consequence of inflammation. However, depression may also add to inflammatory burden through increased sedentary behavior, leading to increased adipose tissue, which is an additional source of inflammation. It is likely that paths linking depression with CVD in SLE are multifactorial as well as bidirectional, and further investigation of these issues is needed.

One limitation of our study is that we did not investigate precisely whether depressive symptoms were directly related to SLE (e.g., a manifestation of CNS lupus) or indirectly related, such as a psychosocial consequence of the life changes brought about by SLE. The cross-sectional design is a limitation that restricts our ability to infer that depression or other risk factors are causally related to vascular disease in SLE. Presumably, vascular changes take place over a long time. Certain risk factors such as adiposity and hypertension may be presumed to be longstanding, but current depressive symptoms may be transient rather than chronic. The CES-D is widely used for quantifying depressive symptoms, in SLE as well as other groups. However, we acknowledge that there are other methods to assess depression, such as the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*[61]. The addition of a diagnostic interview would have the advantage of documenting clinical diagnosis as well as chronicity of depression. Ideally, future studies of the biological and psychological risks for CVD in SLE will include prospective data collection, mood disorder diagnosis in addition to self-report symptoms, and more precise investigation into possible mechanisms linking depression and CVD.

Depression may be associated with premature atherosclerotic disease in SLE through behavioral or biological pathways, or both. In women with SLE, depression is prevalent and is an important influence on physical health and comorbidity in addition to its effect on quality of life. Depression is treatable pharmacologically and through psychotherapy. Attention should be paid to diagnosing and treating depression in SLE, as this should not only contribute to improved quality of life, but possibly improve adherence to medical regimens and physical activity recommendations. Thus, improving management of depression may directly or indirectly influence physical health and overall CVD risk in patients with SLE.

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